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Oral and Maxillofacial Radiology

Analyses of variable panoramic radiographic characteristics of maxillo-mandibular fibrous dysplasia in McCune–Albright syndrome

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OBJECTIVE: Fibrous dysplasia (FD) is a rare skeletal disease caused by activating *GNAS1* gene mutations often found in association with the McCune–Albright syndrome (MAS). Multiple bones may be affected in FD, including maxilla and mandible. Patients with MAS have different endocrinopathies that can further influence bone metabolism. The purposes of this cross-sectional study are to characterize FD panoramic radiographic patterns, and to evaluate the effects of age, endocrinopathies and renal phosphate wasting on radiographic characteristics of maxillo-mandibular FD in MAS.

SUBJECTS AND METHODS: Fifty-one consecutive MAS patients were screened and panoramic radiographs of 43 patients with craniofacial FD were evaluated and analyzed for FD involvement. Clinical chemistries were evaluated for associations between radiographic patterns and age, endocrinopathies or renal phosphate wasting using Fisher's Exact Test.

RESULTS: Four types of radiographic changes were observed: ground glass (granular/condensed trabeculae), radiolucent (lytic), mixed radiolucent/radio-opaque (mixed density) or radio-opaque (sclerotic). Masking or displacement of the maxillary sinus (range: 77.8–86.4%) and mandibular canal (range: 55.6–75.0%) were prevalent in FD sites. Sixty-three percent of the MAS patients had multiple dysregulated endocrine/metabolic functions, the most common were hyperthyroidism, precocious puberty and renal phosphate wasting. There were no statistically significant associations between radiographic patterns and age, endocrinopathies or renal phosphate wasting.

CONCLUSIONS: Maxillo-mandibular FD images in panoramic radiographs fall within a spectrum of four different patterns. Patients with facial asymmetry and any of these radiographic patterns should be promptly referred for further radiographic tests and endocrine evaluation if MAS is suspected.
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Keywords: fibrous dysplasia; radiograph; maxilla; mandible; McCune–Albright syndrome

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Introduction

Fibrous dysplasia (FD) is a rare skeletal disease caused by postzygotic activating mutations of the *GNAS1* gene that encodes for the Gs_{α} subunit of the heterotrimeric G protein complex. It results in constitutive activation of the *adenylyl cyclase* enzyme and overproduction of 3′, 5′-cyclic adenosine monophosphate (cAMP) (Shenker *et al*, 1994). Patients develop bony expansions that contain fibrous tissue and haphazardly distributed irregular woven bone trabeculae (Riminucci *et al*, 1999). It is thought that severity of the disease is related to the time of occurrence of the mutation during embryogenesis. A single bone (monostotic FD) or multiple bones (polyostotic FD) may be affected, craniofacial bones are commonly involved (Lee *et al*, 2002; Riminucci *et al*, 2002) and dental anomalies may be associated (Akintoye *et al*, 2003). Dissemination of *GNAS1* mutations to other tissues may present as the McCune–Albright syndrome (MAS), a triad of polyostotic FD, *café-au-lait* skin hyperpigmentation and autonomous endocrine dysfunction.

Several endocrinopathies may be associated with FD such as precocious puberty (Albright *et al*, 1937), hyperthyroidism (Mastorakos *et al*, 1997), growth hormone excess (Akintoye *et al*, 2002), hypercortisolism

(Kirk *et al*, 1999) and hyperparathyroidism (Cavanah and Dons, 1993). Renal tubulopathy with hypophosphatemia (renal phosphate wasting) is also commonly present in FD/MAS (Collins *et al*, 2001). FD associated with *café-au-lait* skin hyperpigmentation without any endocrinopathy is sometimes referred to as Jaffe–Lichtenstein syndrome (Lichtenstein and Jaffe, 1942; Neville *et al*, 2002).

Radiographic imaging of FD in the maxillofacial region captures the outcome of abnormal bone formation caused by *GNAS1* mutation. Additionally, age, associated endocrinopathies and renal phosphate wasting may affect bone metabolism and growth patterns of the maxilla and mandible. Excess growth hormone or acromegaly in FD/MAS causes disproportionate growth of the craniofacial and maxillofacial skeleton that presents as macrocephaly, facial asymmetry, and mandibular prognathism (Uwaifo *et al*, 2001). Triiodothyroxine (T_3), the active metabolite of thyroid hormone, is necessary for both proliferation and maturation of the growth plate. Therefore, hyperthyroidism accelerates bone development and can lead to osteoporosis (Leger, Thizon de Gaulle and Czernichow, 1993; Ribot, Tremollieres and Pouilles, 1994) and bone loss in the maxilla and mandible (Redman, 2001). Similarly, hypercortisolism or Cushing's syndrome can also precipitate osteoporosis (Redman, 2001). The gonadal hormones (testosterone and estrogen) are hyper-secreted during precocious puberty causing rapid proliferation and maturation of epiphyseal growth plates. Also at puberty, calcium accumulation and biochemical markers of bone turnover are increased (Gertner, 1999). Vitamin D deficiency and osteomalacia, also associated with FD/MAS (Bianco *et al*, 2000; Collins *et al*, 2001; Corsi *et al*, 2003) can cause hypomineralization of maxilla and mandible presenting radiographically as prominent marrow spaces, thinning of the cortical plate and loss of lamina dura (Redman, 2001). Finally, parathyroid hormone and 1, 25 dihydroxyvitamin D_3 (the active metabolite of vitamin D) stimulate osteoclastic bone resorption while calcitonin inhibits osteoclastic bone resorption. Hyperparathyroidism, therefore, causes abnormal bone turn-over and altered radiographic pattern of affected bone that may progress to form circumscribed radiolucent giant cell lesions (Mundy, 1999). These co-factors may further complicate the overall radiographic appearance of FD.

Some references reported that the appearance of maxillo-mandibular FD in panoramic radiographs may vary (Slootweg, 1996; Langland and Langlais, 1997; White and Pharaoh, 2000). These descriptions were made from reports on patient groups limited to children or a few adult patients (El Deeb, Waite and Jaspers, 1979; Kotov *et al*, 1993; Esposito *et al*, 1995; MacDonald-Jankowski, 1999) and did not evaluate the influence of multiple endocrinopathies or renal phosphate wasting which could also alter bone metabolism. In an earlier report that focused on dental characteristics in FD patients, it was reported that imaging of the jaws demonstrated a varied appearance ranging from a ground glass trabeculation to mixed radiolucent/radio-opaque lesions and thinning of the cortical margin (Akintoye *et al*, 2003). It is possible that FD lesions may change their radiographic appearance over time or in response to endocrine dysfunction and/or renal phosphate wasting, but the hypothesis needs to be tested in a large cohort of FD patients. As the panoramic radiograph is the most commonly used imaging technique to evaluate the maxilla and mandible in a dental setting, it is important to determine if certain radiographic findings can predict underlying endocrinopathies, and if the panoramic radiographic pattern is affected by age in FD/MAS patients. To date, there has been no report on the complete spectrum of radiographic findings in maxillo-mandibular FD; neither has there been a report on the possible effects of age and endocrine dysfunction on FD radiographic patterns. Therefore, this cross-sectional study was conducted to characterize the different FD features in panoramic radiographs and to examine the effects of age, endocrinopathies and renal phosphate wasting on radiographic features of maxillo-mandibular FD in MAS.

Patients and methods

Patients

Fifty-one consecutive patients diagnosed with FD/MAS enrolled and participated in an Institutional Review Board-approved clinical protocol at the National Institutes of Health, Bethesda Maryland after giving written informed consent. Diagnosis of FD was established by a combination of clinical history, physical examination, radiographic analyses, and lesional bone biopsy with histopathological and mutation analyses when necessary. The patients' endocrine (gonadal, thyroid, pituitary, adrenal, and parathyroid) and renal functions were also evaluated clinically, biochemically and radiographically. All patients received dental evaluation that included panoramic radiographs taken with Planmeca PM2002CC proline panoramic x-ray unit (Planmeca, Roselle IL, USA).

Analysis of panoramic radiographs

Using the results of head computer tomography (CT) and full body technetium (^{99m}Tc-MDP) bone scan which are more sensitive to detect FD, we identified 43 of 51 (84.3%) patients with FD in the craniofacial region. In this cohort, panoramic radiographs were assessed to characterize maxillo-mandibular FD lesions. Radiographic patterns of the maxilla and mandible bone trabeculae observed in panoramic radiographs were categorized as either: (1) normal, (2) ground glass (granular/condensed trabeculae), (3) radiolucent (lytic), (4) mixed radiolucent/radio-opaque (mixed density) or (5) radio-opaque (sclerotic). Each radiograph was evaluated separately by two trained examiners. The right and left maxilla and mandible were evaluated and categorized separately so that each quadrant was scored as 1, 2, 3, 4, or 5 based on the representative radiographic pattern of each quadrant. We assessed the apparent impact of FD on one radiographic landmark in the maxilla (maxillary sinus) and mandible (mandibular canal); these are vital anatomic structures

that may cause clinical sequelae as a result of encroachment by FD. Within an FD lesion, a radiographically indistinct maxillary sinus floor or a radiographically indistinct or displaced mandibular canal was categorized as 6 (impacted vital anatomic structure). These numbers were assigned to each category for descriptive purposes and carried equal weight. Each panoramic radiograph was evaluated by both examiners; the score assigned to each FD site was discussed and agreed upon by both examiners before being accepted as final. Patients' demographic information, associated endocrinopathies and renal phosphate wasting were also documented.

Statistical analyses

Patients were categorized into three age groups based on tooth eruption pattern as follows: 13 years and below (deciduous and mixed dentition stage), 14–21 years (complete eruption of majority of permanent dentition) and over 21 years (complete eruption/development of all permanent dentition). Results are presented as counts, percentages and mean ± standard deviations. We examined the measure of association between the presence or absence of each of the five radiographic patterns with age and each of the five endocrine/metabolic dysfunctions for each FD location (maxilla and mandible). *P*-values for measure of association were based on Fisher's Exact Test. Because of the 60 simultaneous multiple comparisons (5 radiographic patterns × 6 endocrinopathy parameters × 2 FD locations), we used a Bonferroni adjustment and considered only *P*-values <0.001 to be statistically significant. All analyses were performed using SAS statistical software (Version 8.1; SAS Institute., Cary, NC, USA).

Results

Patient population

Panoramic radiographs of 43 FD patients diagnosed with craniofacial FD were analyzed; 14 (32.6%) patients were males. The age range was 4–80 years (mean 26.6 ± 16.0 years). Nine of 43 (20.9%) were < 13 years, 12 (27.9%) were between 14–21 years and 22 (51.2%) were above 21 years (Table 1).

Radiographic patterns

The present study shows that FD in panoramic radiographs can present in a spectrum of four different radiographic patterns (Table 1): ground glass (condensed/granular trabeculae, Figure 1), radiolucent (lytic, Figure 2), mixed radiolucent/radio-opaque (mixed density, Figure 3) and radio-opaque (sclerotic, Figure 4). The ground glass pattern was most prevalent in the maxilla and mandible of patients below 21 years, but in patients over 21 years, the radio-opaque pattern was most prevalent in the maxilla while mixed radiolucent/radio-opaque pattern was most prevalent in the mandible. No radiolucent FD lesions were observed in the maxilla compared with 12.5% of cases observed in the mandible; these cases were limited to a subgroup of patients within the ages of 14–21 years. Interestingly, among this subgroup, ground glass FD pattern was most prevalent in the maxilla while there was no prevalent pattern in the mandible.

Fibrous dysplasia was observed slightly more often in the maxilla (38 patients, 88.4%) than the mandible (33 patients, 76.7%) but 28 (65.1%) patients presented with FD in both maxilla and mandible. The radiographic pattern of maxillary FD was different from that of mandibular FD in 11 (39.3%) of the 28 patients. An example is the patient illustrated in Figure 2 with ground glass FD lesion in the maxilla but a radiolucent mandibular lesion. Also, FD masked the radiographic outline of the maxillary sinus in more patients (range: 77.8–86.4% in the three age groups) than the mandibular canal (range: 55.6–75.0% in the three age groups) (Table 1, Figures 2–4).

It has been reported that the FD radiographic margin usually blends with adjacent un-affected tissue making

Table 1 Spectrum of panoramic radiographic patterns of fibrous dysplasia (FD) grouped according to age and involvement of vital anatomic structures

Age groups (years)	*N*	*Normal*[b] *Avg.* n *(%)*	*Ground glass Avg.* n *(%)*	*Radiolucent Avg.* n *(%)*	*Mixed radiolucent/ radio-opaque Avg.* n *(%)*	*Radio-opaque Avg.* n *(%)*	*Masked maxillary sinus floor*[c] *Avg.* n *(%)*
Maxilla[a]							
≤13	9	2 (22.2)	3.5 (38.9)	0 (0)	0.5 (5.6)	3 (33.3)	7 (77.8)
14–21	12	4.5 (37.5)	4.5 (37.5)	0 (0)	0 (0)	3 (25.0)	10 (83.3)
>21	22	4.5 (20.5)	7.5 (34.1)	0 (0)	1.5 (6.8)	8.5 (38.6)	19 (86.4)
Age groups (years)	*N*	*Normal*[b] *Avg.* n *(%)*	*Ground glass Avg.* n *(%)*	*Radiolucent Avg.* n *(%)*	*Mixed radiolucent / radio-opaque Avg.* n *(%)*	*Radio-opaque Avg.* n *(%)*	*Masked or displaced mandibular canal*[c] *Avg.* n *(%)*
Mandible[a]							
≤13	9	5.5 (61.1)	2 (22.2)	0 (0)	1.5 (16.7)	0 (0)	5 (55.6)
14–21	12	4.5 (37.5)	2.5 (20.8)	1.5 (12.5)	1.5 (12.5)	2 (16.7)	9 (75.0)
>21	22	11 (50)	1.5 (6.8)	0 (0)	9 (40.9)	0.5 (2.3)	13 (59.09)

N, total number of patients in each age group; Avg. *n* (%), average number (percentage) of patients with either right or left sided FD in each age group.

[a]These data represent average number of patients with FD involvement of right and left sides of maxilla or mandible.

[b]Normal means either (1) normal maxilla but FD present in mandible, (2) normal mandible but FD present in maxilla or (3) normal mandible and maxilla but FD present in other craniofacial bones.

[c]Actual number of patients with FD masking radiographic landmark on one or both sides of maxilla or mandible.

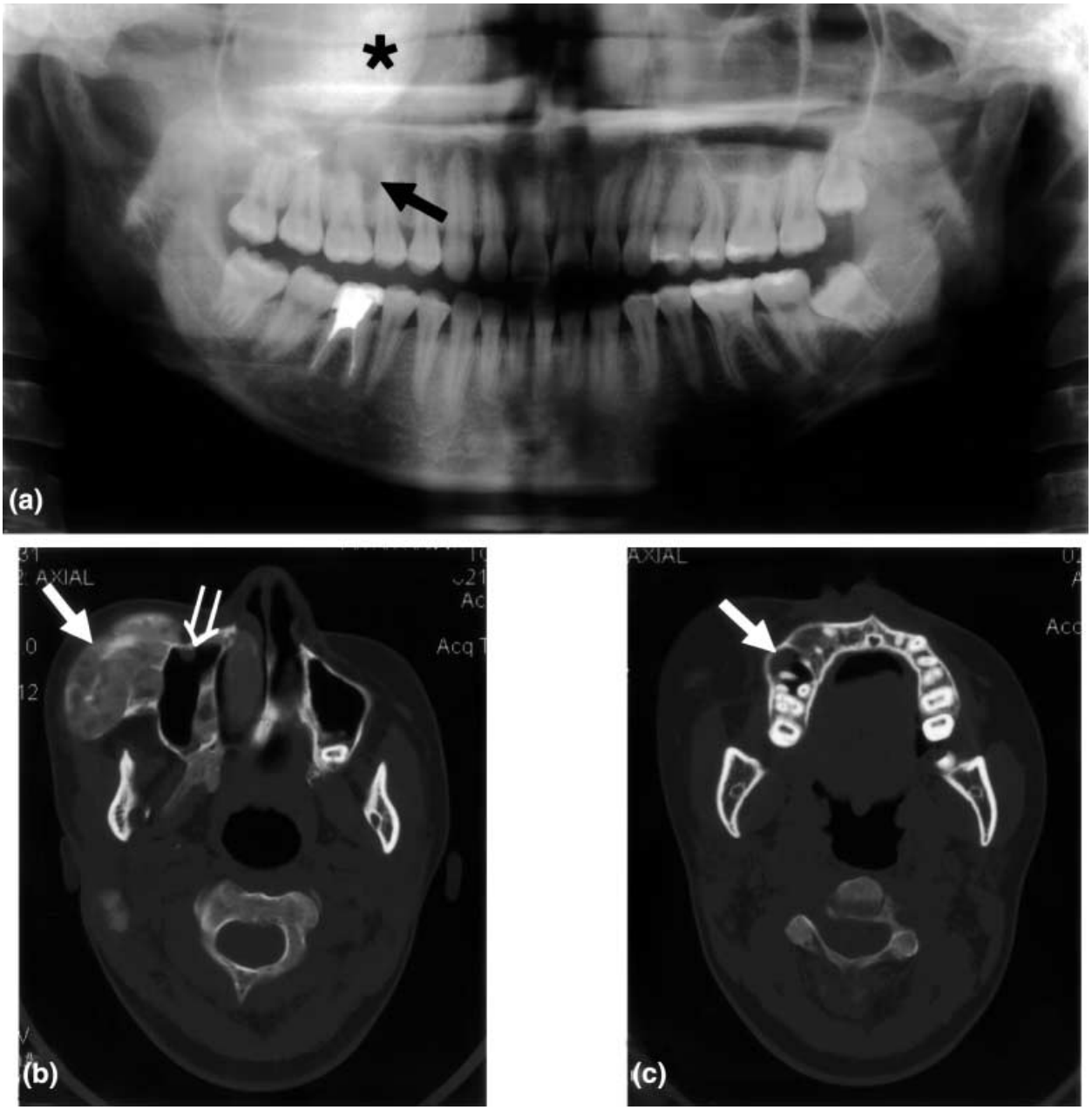

Figure 1 Ground glass pattern. Fibrous dysplasia of right maxilla in a 20-year-old female patient. Panoramic radiograph (**a**) shows ground glass appearance of right maxilla and opacification of maxillary sinus (star, **a**). Note the visible scalloping of sinus floor between roots of teeth nos 1–6 (solid black arrow). Computer tomographic views (bone windows) of same lesion at different levels show ground glass lateral expansion of maxilla (solid white arrow, **b**), a compressed but intact maxillary sinus (open white arrow, **b**) and extension of sinus into the alveolar region between roots of teeth nos 3 and 4 (solid white arrow, **c**)

the outline of the lesion difficult to demarcate (Slootweg, 1996). This blending of FD with normal tissues was observed in ground glass (Figure 1) and radio-opaque FD (Figure 4) lesions. While it was easy to demarcate radiolucent FD lesions (Figure 2), the margins of mixed radiolucent/radio-opaque FD lesions (Figure 3) were partially distinguishable.

Five different dysregulated endocrine/metabolic functions were diagnosed within the group (Figure 5). Hyperthyroidism, precocious puberty and renal phosphate wasting were the most common; 27 (62.8%) patients had multiple endocrinopathies while eight (18.6%) patients had normal endocrine function.

Although there was an apparent trend in radiographic patterns, the results of associations between radiographic patterns and age, endocrinopathy or renal phosphate wasting did not meet strict statistical criteria (Bonferroni adjustment for simultaneous multiple comparisons; $P < 0.001$). We report no statistically significant associations between radiographic patterns and age or endocrinopathy. Similarly, after controlling for age or endocrinopathy in separate analyses, there were no

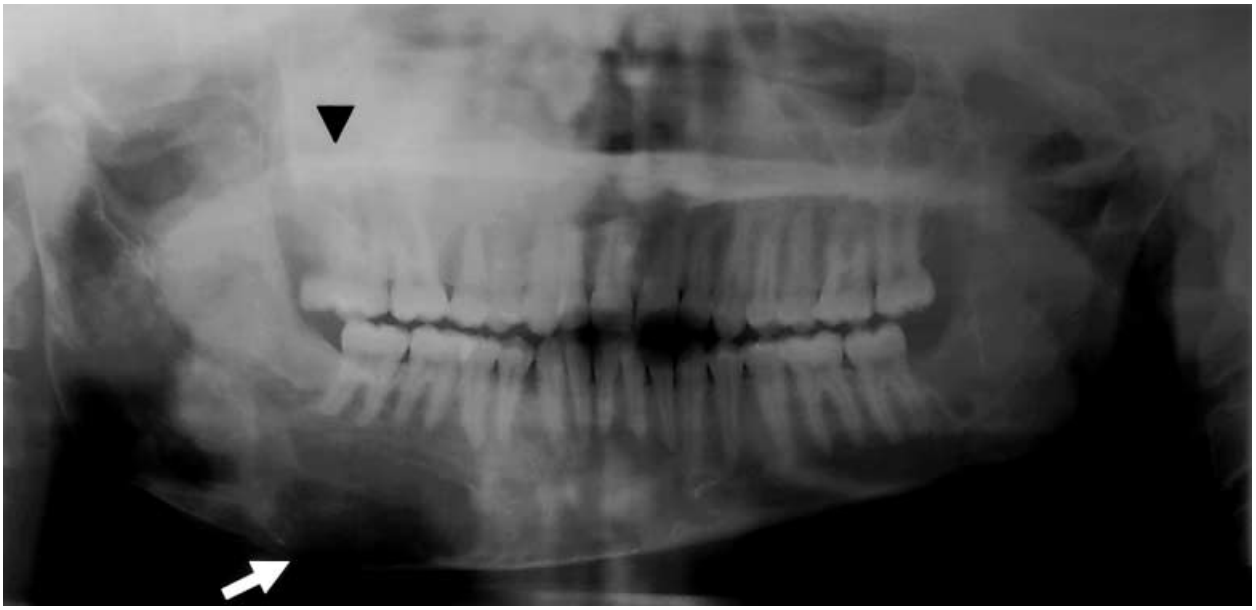

Figure 2 Radiolucent pattern. Fifteen-year-old female patient with fibrous dysplasia (FD) of right maxilla and mandible. Panoramic radiograph shows jaw asymmetry caused by FD expansion of right maxilla and mandible compared with unaffected left side. Mandibular FD is radiolucent (solid white arrow) and extends from the right condyle to the symphysis while maxillary FD is radiopaque (black triangle) and completely masks the maxillary sinus outline. This patient also presented with multiple dysregulated endocrine/metabolic functions that included precocious puberty, hyperthyroidism, renal phosphate wasting and hypovitamin D_3 associated with secondary hyperparathyroidism

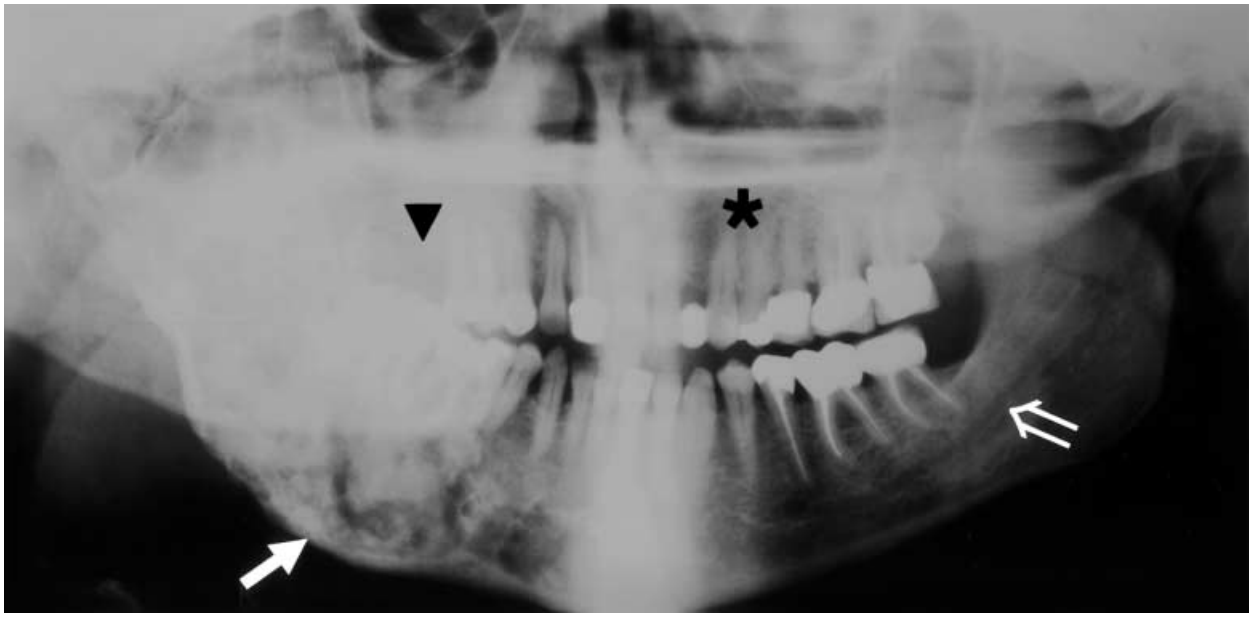

Figure 3 Mixed radiolucent/radio-opaque pattern. Fibrous dysplasia (FD) of maxilla and mandible in a 53-year-old female patient. Panoramic radiograph demonstrated mixed radiolucent/radiopaque (mixed density) pattern of right mandibular FD lesion (solid white arrow) and masking of the outline of right mandibular canal compared with visible mandibular canal outline (open white arrow) of unaffected left body of mandible. Bilateral maxillary FD is radiopaque on right (triangle) and ground glass on the left (star). Endocrinopathies in this patient included hyperthyroidism and hypercortisolism as well as renal phosphate wasting

statistically significant associations between radiographic patterns and endocrinopathy or age respectively.

Discussion

Fibrous dysplasia, especially in MAS, usually affects craniofacial bones (Riminucci *et al*, 2002). It is important for the clinician to identify maxillo-mandibular FD and any associated dental anomalies (Akintoye *et al*, 2003) to adequately manage these patients. Historically, the radiographic presentation of FD is described as 'ground glass' in panoramic radiographs and as 'orange peel' in intra-oral periapical dental radiographs. (White and Pharaoh, 2000; Neville *et al*, 2002). In our FD

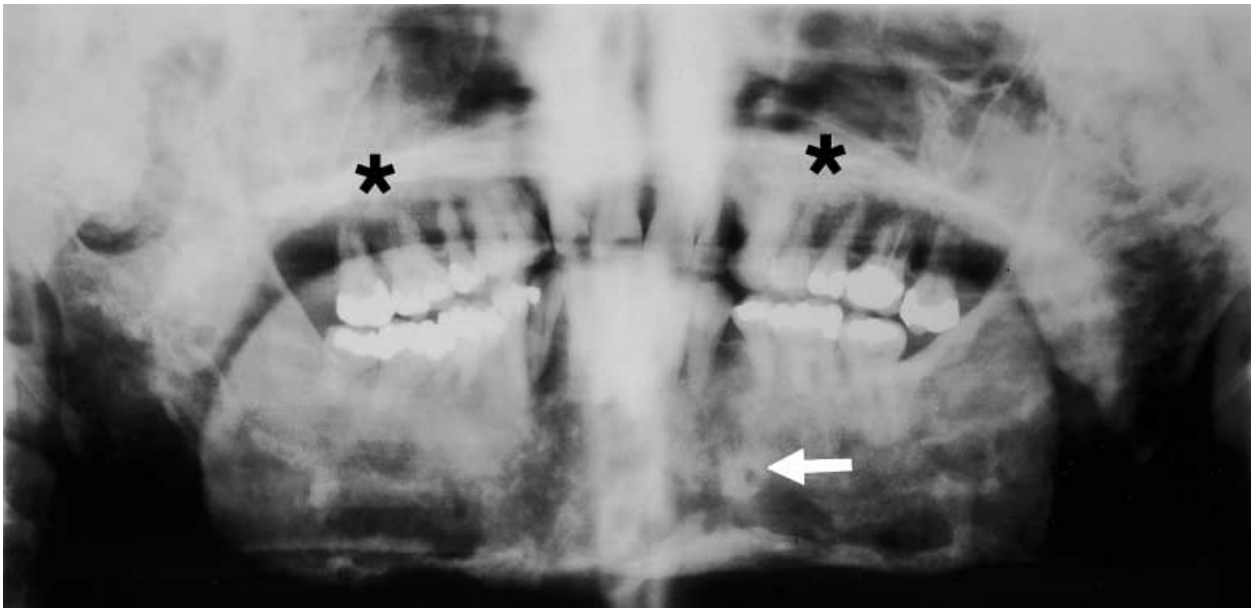

Figure 4 Radio-opaque pattern. Generalized fibrous dysplasia (FD) of maxilla and mandible in a 31-year-old female patient. Panoramic radiograph shows radio-opaque (sclerotic) appearance of FD, expansion of maxilla, mandible, prominence of the hard palate (black stars) and distinct cortication around left mental foramen (white arrow)

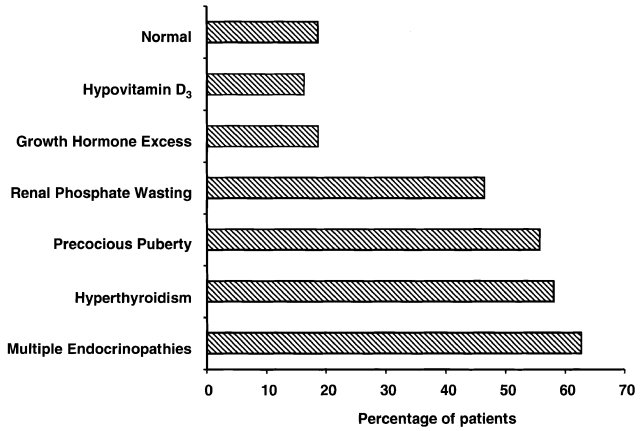

Figure 5 Endocrine functions of patients with fibrous dysplasia ($n = 43$)

cohort, several panoramic radiographic differences were observed, including the classic ground glass pattern. In younger patients (age <21 years), the most common radiographic appearance was ground glass in either the maxilla or mandible, while a radio-opaque pattern was more common in patients over 21 years. While there were no statistical differences in the frequency of patterns in the two age groups, the radio-opaque pattern was often present in the maxilla of FD patients. Also, we did not find a higher frequency of radio-opaque lesions in adult FD patients. As FD can develop at any age, and can change radiographically over time, it is possible that radiographic appearances are associated with age of the particular FD lesion, rather than age of the patient. However, this hypothesis should be tested further in a longitudinal study of this patient group.

No association was detected between radiographic patterns and endocrinopathies or renal phosphate wasting. The presence of single or multiple endocrine/metabolic disorders such as hyperthyroidism, renal phosphate wasting, growth hormone excess and hypovitamin D_3 (progressing to secondary hyperparathyroidism) in FD/MAS alters bone metabolism and may impact FD lesions (Corsi *et al*, 2003). Also, some FD/MAS patients were on several medications including bisphosphonates which have been used to treat FD (Chapurlat and Meunier, 1999). These medications coupled with the individual's response to therapy may have further confounded the FD radiographic pattern.

A radiolucent FD lesion in the maxillo-facial region may be difficult to identify in the maxilla because the maxillary sinus which is a part of the image layer in a panoramic radiograph is also radiolucent and will blend easily with a radiolucent maxillary FD. This masking effect may have influenced our results, as no radiolucent pattern was observed in the maxilla compared with 12.5% in the mandible specifically within age group 14–21 years. Conversely, the greater number of patients with masking of the maxillary sinus compared with the mandibular canal may be explained by the higher prevalence of both ground glass and radio-opaque patterns in the maxilla and the slightly higher number of patients with FD in the maxilla compared with mandible. However, there was no statistically significant association between age and FD impact on vital anatomic structures, or between endocrinopathies/renal phosphate wasting and FD impact on vital anatomic structures.

We are cognizant of potential factors that could affect the appearance of FD in a panoramic radiograph. Histologically, the richly trabecular and vascular nature of the maxilla compared with the more compact

mandible may affect FD imaging in the same individual. We observed that 11 of 28 (39.3%) patients with maxillo-mandibular FD had different radiographic appearances in their maxillary and mandibular FD lesions. Similarly, craniofacial FD is associated with macrocephaly and jaw asymmetry, making it difficult to correctly position an FD patient in a panoramic radiographic machine. These, as well as ability of FD to expand the jaw without distorting the normal anatomic curvilinear shape (Akintoye *et al*, 2003) may affect interpretation of a tomographic image such as a panoramic radiograph.

Fibrous dysplasia is one of several fibro-cemento-osseous lesions that affect the maxillo-facial region. It does not occur exclusively in the jaws such as in cherubism or focal cemento-osseous dysplasia, but like cemento-ossifying fibroma, it presents with different histological patterns (Slootweg, 1996; Su, Weathers and Waldron, 1997a,b). The histological features of FD in the maxilla and mandible are distinct from similar lesions occurring elsewhere in the skeleton; the gnathic bones are sclerotic/hypercellular, the cranial bones are sclerotic/Pagetoid and the axial/appendicular bones demonstrate 'Chinese character' pattern (Riminucci *et al*, 1999). Radiographically, focal cemento-osseous dysplasia is initially radiolucent and shows gradual increase in radiographic density (Waldron, 1993; Langland and Langlais, 1997). FD may behave in similar fashion, demonstrating initial ground glass pattern and progression through a spectrum of four radiographic patterns. Most clinicians are trained to associate ground glass radiographic pattern with FD when reading a panoramic radiograph. Our study indicates that FD has variable radiographic presentations that should not be overlooked. When a lesion is observed in a panoramic radiograph, it is important for the clinician to be aware of the radiographic patterns possible in FD and not exclude FD in the absence of typical ground glass radiographic pattern.

Fibrous dysplasia is not an aggressive lesion, however spontaneous malignant transformation ($< 1\%$) has been reported (Dorfman and Czerniak, 1998) and FD lesions treated with radiation have been known to undergo malignant transformation (Yabut *et al*, 1988; Ruggieri *et al*, 1994). Therefore, FD in the craniofacial region rarely needs treatment except for cosmetic reasons (Lee *et al*, 2002; Riminucci *et al*, 2002). In this cohort, patients with extensive jaw involvement were clinically asymptomatic despite encroachment of FD into the maxillary sinus and masking of the mandibular canal (Figures 2–4). We observed in one patient looping of the mandibular canal within an FD lesion without associated clinical symptoms (result not shown). It is also important to confirm and correlate panoramic radiographic findings using CT imaging. Illustrated in Figure 1, is a panoramic radiograph (Figure 1a) showing ground glass pattern of maxillary FD that partially masked the maxillary sinus. The lesion appeared to compress the sinus in an inferior direction as demonstrated by the scalloping of the sinus floor between the roots of adjacent maxillary teeth. CT images (Figure 1b,c) of the lesion confirmed that the sinus was indeed compressed but not invaded by FD. This pattern supports the non-aggressive behavior of FD.

In summary, maxillo-mandibular FD can present as a spectrum of four patterns in a panoramic radiograph: ground glass (condensed/granular), radiolucent (lytic), mixed radiolucent/radio-opaque (mixed density) and radio-opaque (sclerotic). Each patient's FD radiographic pattern at time of diagnosis may be related to age of the particular FD lesion rather than age of patient, endocrinopathy or renal phosphate wasting, as no association was found between radiographic patterns and these variables. It is important to promptly identify FD lesions both radiographically and histologically so as to properly manage the patient. Dental practitioners should promptly refer such patients for further radiographic evaluation and endocrine testing in cases where MAS is suspected.

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